Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

By the above amendments, claims 1, 8, 19, and 24 are amended and claims 5 and 21 are canceled. Support for these amendments is found in the present application at p. 11, lines 18-24; p. 13, line 12 to p. 14, line 2; and original claims 5 and 21. Claims 1-4, 8-14, 16, 18-20, 24-30, 32, 34, 36, and 38-40 are currently pending. No new matter is introduced.

The rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 under 35 U.S.C. § 112 (1st paragraph) for lack of enablement is respectfully traversed in view of the above amendments.

The specification fully enables a person of skill in the art to practice the claimed methods without undue experimentation. In particular, conditions effective to promote a simultaneous multiphoton excitation of brain tissue by application of radiation may be carried out, according to one preferred embodiment, by thinning (e.g., drilling or abrading) the mammal's skull (page 11, lines 5-6) or, in an alternative embodiment, by performing a craniotomy (page 11, lines 6-7). Suitable wavelengths by which activation of brain tissue is carried out are specifically taught as are various preferred power levels and pulse durations (page 13, line 17 to page 15, line 5). Preferred embodiments of how low energy photons are to be summed are also specifically taught by the present application (page 12, line 24 to page 14, line 12). In addition, the present application includes numerous working examples which describe how to carry out the present invention in exhaustive detail.

As amended, the pending claims themselves are fully enabling. In particular, the claims now specify the power/intensity level (i.e. that capable of being achieved by a titanium sapphire mode locked solid state laser), wavelength (i.e. visible red to infrared region of the light spectrum), pulsing, and pulse width for the activating radiation and the achievement of fluorescence by combining photons. With these features now present in the claims, it is submitted that the U.S. Patent and Trademark Office's ("PTO") grounds for rejecting the claims under 35 U.S.C. § 112 (1st para.) are not proper.

The enablement requirement of 35 U.S.C. § 112 (1st para.) is satisfied by what is disclosed in the specification and not by what is found in the claims:

Environmental Designs, Ltd. v. Union Oil Company of California, 713 F.2d 693, 699 (Fed. Cir. 1983)(citation omitted) states:

> [t]he specification must be sufficiently explicit and complete to enable one skilled in the art to practice the invention, while a claim defines only that which the patentee regards as his invention. The claim, not the specification, measures the invention. …[The] argument that claim 1 must include a limitation found in the specification is thus legally unsound.

In view of the subject matter disclosed in the specification of the present application, it is clear that the present application is enabling.

Since the present application fully enables the claimed invention, the rejection of claims 1-34 under 35 U.S.C. § 112 (1st paragraph) should be withdrawn.

The rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 under 35 U.S.C. § 112 (2nd paragraph) as being incomplete for omitting essential steps is respectfully traversed in view of the above amendments.

The rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 under 35 U.S.C. § 101 for lack of utility is respectfully traversed in view of the above amendments.

The rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 under 35 U.S.C. § 101 for being drawn to non-statutory subject matter is respectfully traversed.

It is the position of the PTO that the rejected claims are not directed to transforming underlying subject matter to a different state or thing, citing *In re Bilski*, 545 F.3d 943, 88 USPQ2d 1385 (Fed. Cir. 2008). However, the method recited in the independent claims is directed to "activating brain tissue of the mammal by application of radiation …to promote a simultaneous multiphoton excitation of the brain tissue and to emit a fluorescence" (claim 1) and "activating brain tissue of a mammal with radiation…to promote a simultaneous multiphoton excitation of the brain tissue and to produce fluorescence" (claim 19). Thus, the underlying subject matter (*i.e.*, the brain tissue) is transformed (*i.e*, to emit a fluorescence). In any event, the claims have been amended to state that the applied radiation is from a laser. Accordingly, the rejection of these claims under 35 U.S.C. § 101 for being drawn to non-statutory subject matter is improper and should be withdrawn.

The rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent Publication No. 2002/0115717 to Gervais et

al., ("Gervais") in view of U.S. Patent No. 6,280,386 to Alfano et al. ("Alfano"), and Christie is respectfully traversed.

Gervais relates to the use of amyloid-targeting imaging agents for imaging amyloid plaques *in vivo*. The amyloid-targeting imaging agents include an amyloid targeting moiety linked to a labeling moiety. The targeting moiety localizes the imaging agents to amyloid plaques, and the labeling moiety allows the imaging agents to be visualized by ultrasound imaging, computed tomography imaging, magnetic resonance imaging, nuclear medicine imaging, optical imaging, and elastography. Labeling moieties taught by Gervais for use in optical imaging include fluorescent or colored dyes. There is no suggestion in Gervais of using simultaneous multiphoton excitation, as claimed.

Alfano teaches an imaging system in which images of objects within tissue are enhanced by applying a contrast agent to a sample to be imaged, thereby forming a luminous object. The tissue is illuminated and 2 image signals are recorded. These 2 image signals are subtracted to minimize an image component resulting from the tissue and to enhance the image component resulting from the luminous object. Alfano also fails to suggest the use of simultaneous multiphoton excitation.

The outstanding office action acknowledges that Gervais and Christie do not teach the use of multiphoton excitation. The use of simultaneous multiphoton excitation in accordance with the present invention has a number of very important benefits. In particular, multiphoton excitation has a very high resolution capability, on the order of one micrometer (page 20, lines 26-29 of the present application), and can reach unprecedented depths (page 27, lines 15-18 of the present application). In addition to permitting high resolution imaging of living tissue, multiphoton excitation has the unique advantage of incurring only minimal photodamage or toxicity on the living tissue being imaged (page 25, lines 25-26 of the present application). These unique features of multiphoton excitation imaging make possible the detection and observance of certain Alzheimer's Disease-like lesions that are otherwise undetectable with prior art imaging technologies (page 25, lines 21-25 and page 46, lines 11-12 of the present application). Multiphoton excitation methods of imaging also provide the opportunity to evaluate a relatively large 3-dimensional reconstruction of the cerebral vasculature (page 32, lines 17-19 of the present application). Additionally, multiphoton excitation of fluorophores provides a method of imaging with improved background

discrimination and reduces photobleaching of the fluorophores (page 12, line 19 to page 13, line 8 of the present application).

Christie is cited to disclose the use of multiphoton imaging to analyze Alzheimer's Disease neuropathology. As set forth in the Declaration of Watt W. Webb Under 37 C.F.R. § 1.132, filed by mail on September 7, 2004 ("First Webb Declaration"), Christie begins by citing a number of advantages if this approach were to be successful (First Webb Declaration ¶ 7). However, Christie does not provide an enabling disclosure of the present invention.

A reference that teaches an inoperative device may be "prior art for all that it teaches." *Beckman Instruments v. LKB Produkter AB*, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989); MPEP § 2121.01. However, in view of all of the deficiencies in Christie noted in the First Webb Declaration, those skilled in the art would not, based on Christie, have been able to carry out imaging of Alzheimer's Disease neuropathology using multiphoton excitation (First Webb Declaration ¶ 12). Moreover, neither Gervais, Alfano, nor Christie teach application of radiation through an opening or a thinned portion of the mammal's skull, where the radiation is at an intensity level capable of being achieved by a titanium sapphire mode locked solid state laser, where the radiation has a wavelength in the visible red to the infrared region of the light spectrum and is pulsed at a pulse width between about 10^{-9} to 10^{-15} second, and where the fluorescence characteristic is achieved by combining photons.

Since Gervais and Alfano fail to teach or suggest the use of simultaneous multiphoton excitation of brain tissue for detection of neurodegenerative diseases and Christie does not provide an enabling disclosure of how to carry out such multiphoton excitation, the rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 for obviousness over Gervais in view of Alfano and Christie is again improper and should be withdrawn.

The rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 6,329,531 to Turner et al. ("Turner") in view of U.S. Patent Application Publication No. 2003/0236458 to Hochman ("Hochman") and Christie is respectfully traversed.

As discussed by the Declaration of Watt W. Webb under 37 C.F.R. § 1.132 filed on December 31, 2008 ("Second Webb Declaration"), Turner relates to *in vivo* and *in vitro* diagnosis of neurodegenerative diseases such as Alzheimer's Disease by means of near infra-red

radiation (Second Webb Declaration ¶ 8). According to the *in vivo* methods of Turner, one or more dye compounds are fed to the tissue being diagnosed and light from the near-infrared spectral region is irradiated (*Id.*). The non-absorbed, scattered light and/or scattered fluorescence radiation emitted by the dye is recorded simultaneously/individually (*Id.*). Preferred methods are where the tissue irradiates over a large surface, and the fluorescence radiation that is resolved locally is visualized by imaging with a CCD camera or the tissue areas that are to be imaged are rastered with a fiber optic light guide and the signals that are received are converted numerically into a synthetic image (*Id.*). Fluorescence can also be evaluated spectrally and/or by phase selection, as well as in a steady-state manner and/or in a time-resolved manner (*Id.*).

Hochman teaches methods for optically detecting physiological properties in an area of interest by detecting changes in the intrinsic or extrinsic optical properties of tissue (Second Webb Declaration ¶ 9). This involves optically detecting blood flow changes, blood characteristics, and blood vessel abnormalities, as well as determining the presence and location of abnormal or pathological tissue for identifying and mapping the margins of abnormal tissue (*Id.*). According to Hochman, these methods may be used to identify physiological conditions associated with and to evaluate diagnosis of Alzheimer's Disease and other neurodegenerative disorders (*Id.*). Optical detection may involve invasive or semi-invasive systems and may be continuous or non-continuous (*i.e.*, pulsed) (*Id.*). Data sets from patients can be compared to standard or control data representative of optical properties indicative of various disease states or conditions (*Id.*). Longer wavelengths (e.g., approximately 800 nm) can be employed to analyze deeper areas of tissue (*Id.*).

Turner and Hochman disclose the use of a class of colorant signal molecules (Second Webb Declaration ¶ 10). To the extent these references discuss how they are used, their achievement of fluorescent excitation does not result in a non-linear process like two-photon or multiphoton excitation (*Id.*). The dyes utilized by Turner and Hochman absorb low-energy infrared radiation photons to excite the dye molecules to the low energies corresponding to the infrared photons (*Id.*). In contrast, two-photon or multiphoton excitation absorbs two or more infrared photons virtually simultaneously to excite a molecule to an energy level corresponding to the sum of the energies of the two or more infrared photons (*Id.*). These energy levels can then be high enough to be released by emission of visible or even ultraviolet fluorescence (*Id.*). Since the procedures used by Turner and Hochman do not achieve such a high energy of

excitation, it is apparent that they do not carry out simultaneous multiphoton excitation, in accordance with the present invention (*Id.*).

As the PTO agreed on page 2 of the outstanding office action, neither Turner nor Hochman teach or suggest the method of the present invention involving detecting plaques characteristic of neurodegenerative disease using multiphoton excitation. Christie is relied upon to overcome this deficiency. However, for the reasons noted above with regard to the preceding rejection, Christie does not provide an enabling disclosure of how to image Alzheimer's Disease neuropathology using multiphoton excitation.

Since the combination of Turner and Hochman fail to teach or suggest the use of simultaneous multiphoton excitation of brain tissue and Christie does not provide an enabling disclosure of how to carry out such multiphoton excitation, the rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36, and 38-40 under 35 U.S.C. § 103(a) for obviousness over these references is improper and should be withdrawn.

In view of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited

Respectfully submitted,

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